SUPPORT FOR THE AMENDMENTS

Applicants have amended Claim 37 to incorporate the limitations of canceled Claims 11 and 33. Accordingly, support for amended Claim 37 can be found in Claims 11, 33 and 37, as previously presented. Applicants have amended Claim 38 to include a limitation which has been deleted from amended Claim 37. Thus, support for amended Claim 38 can be found in Claim 37, as previously amended. Applicants have also added new Claim 39. Support for new Claim 39 can be found on page 10, lines 30-31, of the specification. Claims 18-21, 28, and 29 have been amended for clarity. Support for amended Claims 18-21, 28, and 29 can be found in the same claims, as previously presented.

No new matter has been added. Claims 14, 15, 18-25, 28, 29, 31, 32, and 36-39 are active in this application.

REMARKS/ARGUMENTS

The present claims relate to processes for the preparation of a dry powder formulation for the pulmonary administration of a micronized drug by means of a dry powder inhaler, said process comprising mixing coarse carrier particles having a diameter which lies between 20 and 1000 μm with fine carrier particles having a diameter of less than 10 μm and magnesium stearate in an amount of 0.05 to 2%.

The inventors have discovered that the presently claimed process provides a dry powder for the pulmonary administration of micronized drugs for which the respirable fraction of the delivered dose of the drug is improved by maintaining good flowability characteristics of the powder, *i.e.*, characterized by a Carr's index of less than 25 (*see*, Claim 29).

Thus, the technical problem which is solved by the presently claimed process is the reduction of the interparticle forces between the micronized active drug and the carrier that

can affect the availability of the drug to the respiratory tract, by maintaining suitable flowability properties.

As pointed out from page 2, lines 26 onwards, of the present specification, drug particles have to be in micronized form to be able to reach the lower lungs, but the finer the particles are, the stronger the interparticle cohesion forces are, so that the drug particles tend to agglomerate or adhere to the surface of carrier particles. The strong interparticle forces may act to prevent the separation of the micronized drug particles from the surface of the coarse carrier, during inhalation, and, thus, compromise the availability of the drug to the respiratory tract (*see*, page 3, lines 25-30, of the present specification). Moreover, cohesion forces reduce the flowability of the particles, thus, favoring their adhesion to the walls of the powder inhaler (*see*, page 2, lines 29-33, of the present specification). Such drawbacks have a detrimental effect on the respirable fraction of the active ingredient delivered dose (*see*, page 3, lines 3-12, of the present specification).

The solution offered by the presently claims is to provide a process for preparing a dry powder formulation which is free flowing and capable of delivering a suitable amount of medicament to the lungs.

According to Claim 1, the process comprises mixing coarse carrier particles having a diameter between 20 and 1000 μm with fine carrier particles having a diameter of less than 10 μm and from 0.05% to 2% of magnesium stearate.

In Example 1 of the present application, it is shown that a powder formulation which comprises coarse carrier particles having a diameter comprised between 90 and 150 μm and fine carrier particles having a diameter of less than 10 μm (*see*, Fig. 1 and Table 1) are provided with a good flowability and can deliver a higher fine particle fraction of active ingredient with respect to a standard preparation which does not contain the finer particles

(*see*, Table 2 on page 13). The flowability was evaluated from the Carr's Index and by using a Flodex tester.

In Example 3 the preparation of a BDP/lactose/magnesium stearate ternary mixture is reported. The lactose carrier is the same of Example 1 and therefore is made of a coarse fraction of particles having a diameter comprised between 90 and 150 μm and a fine fraction of particles having a diameter of less than 10 μm. Lactose particles were mixed with 0.25% by weight of magnesium stearate, and the micronized active ingredient added to the mixture. The flowability characteristics as well as the aerosol performances are reported in Table 4 and show the good characteristics of flowability and the significant increase of the fine particle fraction, with respect to a comparative preparation which does not contain the fine particle fraction.

The rejection of Claims 11, 14, 15, 18-33, 35, and 36 under 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,153,224 (Staniforth) and U.S. Patent No. 6,284,287 (Sarlikiotis et al) and the rejection of Claims 37 and 38 under 35 U.S.C. § 103(a) in view of Staniforth and Sarlikiotis et al are respectfully traversed.

As pointed out before, it is well known to those skilled in the art that the flowability of a powder is such an important property in that nearly all handling processes are affected to a greater or lesser extent. In the case of dry powder aerosol formulations, the flowabilities of both the drug and carrier particles play an important role in mixing, capsule-filling, metering of the dose, and aerosolization. The flowability of a powder is, *inter alia*, a function of particle size, size distribution, and interparticulate forces.

Staniforth discloses a dry powder that includes an active compound, a carrier with an aerodynamic diameter of 20-1000 microns, and an additive. The preferred range of particle sizes lies in the range of 60 μm to 180μm. Staniforth also discloses a "gentle" milling

process to treat the surface of the carrier particles wherein smaller grains of the carrier material are produced.

At column 15, lines 28-31, Staniforth discloses that a "***Carr's index of less than 25 is usually taken to indicate good flow characteristics,***" while a "***Carr's index greater than 40 indicates poor flow characteristics.***" However, the carrier particles of Example 3 of Staniforth, comprising coarse lactose particles having small grains reattached to their surface and 1 % by weight leucine particles, have a poor flowability.

In sharp contrast, the Carr's index values reported in Tables 2, 3, and 4 of the present application demonstrate that the presently claimed powder formulations do, in fact, exhibit good flowability properties. Therefore, the fraction of fine particles having a diameter below 10 μm of the presently claimed process allows the modulation of the interparticle forces between the carrier particles and the micronised drug (*see*, page 6, lines 21-25, of the present specification), thereby allowing a better dispersion of the active particles in the respiratory tract and improving the respirable fraction of the active compound, without affecting the flowability of the powder (*see*, page 7, lines 13-18 and 31-34, of the present specification).

Staniforth discloses a dry powder for use in an inhaler that includes an active agent with an aerodynamic diameter of 0.1-5 microns, a carrier powder with an aerodynamic diameter of 20-1000 microns, and less than 2% of an additive. Staniforth also discloses various additives for use, including magnesium stearate. However, Staniforth does not disclose the specific formulation resulting from the process of the present claims, which comprises coarse carrier particles having a diameter between 20 and 1000 μm, a fine carrier particles having a diameter below 10 μm and magnesium stearate.

Instead, Staniforth actually teaches away from the use of a fine carrier fraction having a diameter below 10 μm: "***Small particles with a diameter of less than 10 μm may be***

deposited on the wall of the delivery device and have poor flow and entrainment properties leading to poor dose uniformity" (*see*, column 2, lines 13-16).

Moreover, in Staniforth, magnesium stearate is not the additive of choice, but merely a material that may be used but is not preferred (*see*, col. 2, lines 61-62), that according to example 13, when added in an amount of 1.5% to a powder composition may provide satisfactory results in terms of a respirable fraction, ***but does not meet the other important requirement of retaining homogeneity*** (*see*, col. 24, lines 2-7). Indeed, Staniforth states that "***It is particularly advantageous for the additive material to comprise an amino acid***" and that ***leucine is the preferred amino acid and the preferred additive*** (*see*, col. 5, lines 12-18 and lines 25-26). Therefore, Staniforth actually teaches away from the use of magnesium stearate in the composition.

As pointed out before, Staniforth discloses, at col. 15, line 29, that a Carr's index of less than 25 provides good flow characteristics. As a matter of fact, the carrier of Staniforth shows a Carr's index of 36.4, which is only slightly improved to 35.6 or 32.1 by the addition of 1 % leucine and 1 % leucine in combination with the milling treatment, respectively. In other words, even the preferred carrier of Staniforth has a very poor flowability.

On the other hand it is reported in the literature that carriers such as lactose can undergo chemico-physical alterations, when subjected to mechanical stresses such as milling (*see*, page 7, lines 1-4, of the present specification) and this kind of treatment may have adversely affected the flowability of the carrier of Staniforth. To the contrary, the formulations afforded by the presently claimed process, which comprise fine particles with a diameter below 10 microns and magnesium stearate as additive are endowed with very good flowability properties. The good flow characteristics of the particles allow a better reproducibility and uniformity of the dose, and the reduction of interparticle forces results in

a more efficient release of the active ingredient particles on the delivery of the dose, providing for a significant increase of the respirable fraction.

Sarlikiotis et al offers a different solution, by suitably mixing the active compound with the carrier (or excipient) so that the active compound particles adhere to the carrier (excipient) particles, thereby resulting in almost ***round excipient particles coated with active compound*** (*see*, col. 2, lines 56-64). The particles so obtained are defined as "soft pellets" and are constituted of ***agglomerates*** of the constituents (*see*, col. 4, lines 60-65).

Sarlikiotis et al does not teach or suggest preparing a dry powder for pulmonary inhalation by mixing fine carrier particles having a diameter below 10 μm with coarse carrier particles in order to decrease the interparticle forces between the active substance and the carrier particles and even less to add an additive in order to further improve the respirable fraction of the delivered drug. On the contrary, Sarlikiotis et al actually teaches away from the use of additives or auxiliary substances:

> ***Additionally, at present most of the pharmaceutically customary auxiliaries cannot be used in pharmaceutical forms for inhalation, as the toxicological behavior of these substances on pulmonary administration is still largely unknown.***

See, col. 1, lines 43-48.

Therefore, there were no reasons or hints for those skilled in the art, at the time of the invention, to combine the teaching of Staniforth (which discloses that the preferred additive is an amino acid, the most preferred one being leucine and which also discloses that particles with a diameter of less than 10 μm can lead to poor dose uniformity) with Sarlikiotis et al that discourages against the use of additives and only discloses mixing an active ingredient with a carrier (or excipient) to coat the carrier crystals with the active compound forming agglomerates defined as "soft pellets."

In any case, the combined teaching of Staniforth and Sarlikiotis et al cannot lead to the process for the preparation of the specific composition of the dry powder formulations as presently claimed.

For all of these reasons, the rejections are improper and should be withdrawn.

The rejection of Claims 11, 14, 15, 18-33, and 35-38 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 1-21 of U.S. Patent No. 6,641,844 (Musa et al) is being obviated by the filing herewith of a duly executed Terminal Disclaimer over Musa et al. Accordingly, the rejection is no longer tenable and should be withdrawn.

Applicants submit that the present application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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